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5 January 2004

VIA EXPRESS MAIL, WITH RETURN POSTCARD ENCLOSED

PCT International Application Processing Div.
USPTO International Division
Assistant Commissioner for Patents
Mail Stop PCT
PO Box 1450
Alexandria, VA 22313-1450

Re: International Application No. PCT/US03/17825
Title: METHODS OF DIAGNOSING AND TREATING DIABETES AND INSULIN RESISTANCE
Applicant: METABOLEX, INC.
International Filing Date: 04 June 2003
Express Mail Label No.: EV 332 022 204 US
Date of Mailing: 05 January 2004
Our File No.: 16325-140PC

Dear Officer:

Enclosed is the Chapter II Demand for the above-referenced application. Also enclosed are twelve (12) substitute pages 25, 45, 109, 110, 111, 112, 128, 129, 130, 131, 132 and 133 of the specification submitted as an Article 34 Amendment. The changes to the pages are insertions of SEQ ID:NOs and correction of typographical errors. These changes do not go beyond the disclosure of the application as filed.

Thank you for your attention to this matter.

Respectfully submitted,

TOWNSEND and TOWNSEND and CREW LLP

Matthew E. Hinsch
Reg. No. 47,651

Enclosures:
Chapter II Demand
Twelve (12) Sub. Specification pages (25,45,109,110 111,112,128,129,130,131,132,133
One hundred and sixty-two (162) pages of Sequence Listing
Diskette and Statement
Transmittal Letter
Postcard

60111100 v1

The demand must be filed directly with the competent International Preliminary Examining Authority; if two or more Authorities are competent, with the one chosen by the applicant; the full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ US

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only

Identification of IPEA	Date of receipt of DEMAND

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION

Applicant's or agent's file reference: 16325-140PC

International application No.	International filing date (*day/month/year*)	(Earliest) Priority date (*day/month/year*)
PCT/US03/17825	04 June 2003 (04.06.03)	04 June 2002 (04.06.02)

Title of invention

METHODS OF DIAGNOSING AND TREATING DIABETES AND INSULIN RESISTANCE

Box No. II APPLICANT(S)

Name and address: (*Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.*)

METABOLEX, INC.
3876 Bay Center Place
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United States of America

Telephone No.: 510.293.8800
Facsimile No.: 510.293.9090
Teleprinter No.:
Applicant's registration No. with the Office

State (*that is, country*) of nationality:	State (*that is, country*) of residence:
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IE	US

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State (*that is, country*) of nationality:	State (*that is, country*) of residence:
BE	US

☒ Further applicants are indicated on a continuation sheet.

International application No.
PCT/US03/17825

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

Name and address: (*Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.*)

LAVAN, Brian
2020 Lawton Street
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State (*that is, country*) of nationality:	State (*that is, country*) of residence:
GB	US

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MOODIE, Shonna
2091 Golden Gate Avenue
San Francisco, CA 94115
United States of America

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GB	US

Name and address: (*Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.*)

WATERS, Steve
1 Lobelia Lane
San Ramon, CA 94583
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State (*that is, country*) of nationality:	State (*that is, country*) of residence:
US	US

Name and address: (*Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.*)

WONG, Chi-Wai
28073 Thorup Lane
Hayward, CA 94542
United States of America

State (*that is, country*) of nationality:	State (*that is, country*) of residence:
CN	US

☐ Further applicants are indicated on a continuation sheet.

International application No.
PCT/US03/17825

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is ☒ agent ☐ common representative

and ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.

☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.

☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: (*Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.*)

HINSCH, Matthew E
TOWNSEND AND TOWNSEND AND CREW LLP
Two Embarcadero Center, 8th Floor
San Francisco, California 94111-3834
United States of America

Telephone No.: 415-576-0200

Facsimile No.: 415-576-0300

Teleprinter No.:

Agent's registration No. with the Office: 47,651

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

1. The applicant wishes the international preliminary examination to **start on the basis of**:

☒ the international application as originally filed

the description	☐	as originally filed
	☒	as amended under Article 34
the claims	☒	as originally filed
	☐	as amended under Article 19 (together with any accompanying statement)
	☐	as amended under Article 34
the drawings	☒	as originally filed
	☐	as amended under Article 34

2. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.

3. ☐ The applicant wishes the start of the international preliminary examination **to be postponed** until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). (*This check-box may be marked only where the time limit under Article 19 has not yet expired.*)

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: ENGLISH

☒ which is the language in which the international application was filed.

☐ which is the language of a translation furnished for the purposes of international search.

☐ which is the language of publication of the international application.

☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The applicant hereby **elects all eligible States** (*that is, all States which have been designated and which are bound by Chapter II of the PCT*)

excluding the following States which the applicant wishes **not to elect**:

Sheet No. 4

International application No.
PCT/US03/17825

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

				For International Preliminary Examining Authority use only: received	not received
1. translation of international application	:		sheets	☐	☐
2. amendments under Article 34	:	12	sheets	☐	☐
3. copy (or, where required, translation) of amendments under Article 19	:		sheets	☐	☐
4. copy (or, where required, translation) of statement under Article 19	:		sheets	☐	☐
5. letter	:	1	sheets	☐	☐
6. other (*specify*)	:		sheets	☐	☐

The demand is also accompanied by the item (s) marked below:

1. ☒ fee calculation sheet
2. ☐ original separate signed power of attorney
3. ☐ original general power of attorney;
4. ☐ copy of general power of attorney; reference number, if any:
5. ☐ statement explaining lack of signature
6. ☒ sequence listing in computer readable form
7. ☐ tables in computer readable form related to sequence listings
8. ☐ other (*specify*) Transmittal Letter, Postcard, Diskette

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

X _____

Matthew E. Hinsch
TOWNSEND AND TOWNSEND AND CREW LLP
USPTO Reg. No.: 47,651
Applicants' Agent

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:
2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):
3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply. ☐ The applicant has been informed accordingly.
4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.
5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

2. Size Differential Filtration

[0085] Based on a calculated molecular weight, a protein of greater and lesser size can be isolated using ultrafiltration through membranes of different pore sizes (for example, Amicon or Millipore membranes). As a first step, the protein mixture is ultrafiltered through a membrane with a pore size that has a lower molecular weight cut-off than the molecular weight of the protein of interest. The retentate of the ultrafiltration is then ultrafiltered against a membrane with a molecular cut off greater than the molecular weight of the protein of interest. The recombinant protein will pass through the membrane into the filtrate. The filtrate can then be chromatographed as described below.

3. Column Chromatography

[0086] The proteins of interest can also be separated from other proteins on the basis of their size, net surface charge, hydrophobicity and affinity for ligands. In addition, antibodies raised against proteins can be conjugated to column matrices and the proteins immunopurified. All of these methods are well known in the art.

[0087] Immunoaffinity chromatography using antibodies raised to a variety of affinity tags such as hemagglutinin (HA), FLAG, Xpress, Myc, hexahistidine(SEQ ID NO:113) (His), glutathione S transferase (GST) and the like can be used to purify polypeptides. The His tag will also act as a chelating agent for certain metals (e.g., Ni) and thus the metals can also be used to purify His-containing polypeptides. After purification, the tag is optionally removed by specific proteolytic cleavage.

[0088] It will be apparent to one of skill that chromatographic techniques can be performed at any scale and using equipment from many different manufacturers (*e.g.*, Pharmacia Biotech).

IV. DETECTION OF POLYNUCLEOTIDES OF THE INVENTION

[0089] Those of skill in the art will recognize that detection of expression of polynucleotides and polypeptides of the invention has many uses. For example, as discussed herein, detection of levels of polynucleotides and polypeptides of the invention in a patient is useful for diagnosing diabetes or a predisposition for at least some of the pathological effects of diabetes. Moreover, detection of gene expression is useful to identify modulators of expression of polynucleotides and polypeptides of the invention.

interleukin receptors, immunoglobulin receptors and antibodies, the cadherin family, the integrin family, the selectin family, and the like; *see, e.g.,* Pigott & Power, *The Adhesion Molecule Facts Book I* (1993)). Similarly, toxins and venoms, viral epitopes, hormones (*e.g.*, opiates, steroids, *etc.*), intracellular receptors (*e.g.*, which mediate the effects of various small ligands, including steroids, thyroid hormone, retinoids and vitamin D; peptides), drugs, lectins, sugars, nucleic acids (both linear and cyclic polymer configurations), oligosaccharides, proteins, phospholipids and antibodies can all interact with various cell receptors.

[0165] Synthetic polymers, such as polyurethanes, polyesters, polycarbonates, polyureas, polyamides, polyethyleneimines, polyarylene sulfides, polysiloxanes, polyimides, and polyacetates can also form an appropriate tag or tag binder. Many other tag/tag binder pairs are also useful in assay systems described herein, as would be apparent to one of skill upon review of this disclosure.

[0166] Common linkers such as peptides, polyethers, and the like can also serve as tags, and include polypeptide sequences, such as poly-Gly sequences of between about 5 and 200 amino acids (SEQ ID NO:114). Such flexible linkers are known to those of skill in the art. For example, poly(ethylene glycol) linkers are available from Shearwater Polymers, Inc., Huntsville, Alabama. These linkers optionally have amide linkages, sulfhydryl linkages, or heterofunctional linkages.

[0167] Tag binders are fixed to solid substrates using any of a variety of methods currently available. Solid substrates are commonly derivatized or functionalized by exposing all or a portion of the substrate to a chemical reagent that fixes a chemical group to the surface that is reactive with a portion of the tag binder. For example, groups that are suitable for attachment to a longer chain portion would include amines, hydroxyl, thiol, and carboxyl groups. Aminoalkylsilanes and hydroxyalkylsilanes can be used to functionalize a variety of surfaces, such as glass surfaces. The construction of such solid phase biopolymer arrays is well described in the literature (*see*, *e.g.*, Merrifield, *J. Am. Chem. Soc.* 85:2149-2154 (1963) (describing solid phase synthesis of, *e.g.*, peptides); Geysen *et al., J. Immun. Meth.* 102:259-274 (1987) (describing synthesis of solid phase components on pins); Frank and Doring, *Tetrahedron* 44:60316040 (1988) (describing synthesis of various peptide sequences on cellulose disks); Fodor *et al., Science*, 251:767-777 (1991); Sheldon *et al., Clinical Chemistry* 39(4):718-719 (1993); and Kozal *et al., Nature Medicine* 2(7):753759 (1996) (all describing

CTCATGAAACCCAGTCACGTCATTGTGGAGACCATGATGTGAGGTCCGGGCTGTGTGACCGGCGCCGCTTTCCTG
CCGTTTACTAACCTTAGATTCTCCTAGGACCAGGTTTACAGAGCTTTATATTTGTACTAGGATTTTTTTTTTAAT
TGTCACAGAAAATGTTACTCTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTTTCGTGTGTG
TCTGTATATGTGTATTTTGTTTTATTTGGGGGATTATTTTGTACAAAAAGAAAACCCATGGGCCTATGTCCTGGG
GGGAGAGGATGGACTTTCATATTGATTTTGATGTATTTTATGGGAACTTGGTAAATTTTTCTTTGTATTTTTTTA
ACATATAACTATATATAGAGTCTGTCATACACTTTGCCACTTGAATTGGTCTTGCCAGCAACGGATCTCGTTTTT
TGTTTTTTGTTTTTTTTTCAAAAGCAATTCTTCGGTGCTTACATAGCTGGCAGAGAGTTCTGCCCAAAAACAAAT
GAAAAAAAAAAAAA

SEQ ID NO:66 Rat Taurine Transporter polypeptide sequence

accession:gi8394318

MATKEKLQCLKDFHKDILKPSPGKSPGTRPEDEADGKPPQREKWSSKIDFVLSVAGGFVGLGNVWRFPYLCYKNG
GGAFLIPYFIFLFGSGLPVFFLEVIIGQYTSEGGITCWEKICPLFSGIGYASIVIVSLLNVYYIVILAWATYYLF
QSFQKDLPWAHCNHSWNTPQCMEDTLRRNESHWVSLSAANFTSPVIEFWERNVLSLSSGIDHPGSLKWDLALCLL
LVWLVCFFCIWKGVRSTGKVVYFTATFPFAMLLVLLVRGLTLPGAGEGIKFYLYPNISRLEDPQVWIDAGTQIFF
SYAICLGAMTSLGSYNKYKYNSYRDCMLLGCLNSGTSFVSGFAIFSILGFMAQEQGVDIADVAESGPGLAFIAYP
KAVTMMPLPTFWSILFFIMLLLLGLDSQFVEVEGQITSLVDLYPSFLRKGYRREIFIAIVCSISYLLGLTMVTEG
GMYVFQLFDYYAASGVCLLWVAFFECFVIAWIYGGDNLYDGIEDMIGYRPGPWMKYSWAVITPALCVGCFIFSLV
KYVPLTYNKVYRYPDWAIGLGWGLALSSMVCIPLVIVILLCRTEGPLRVRIKYLITPREPNRWAVEREGATPFHS
RATLMNGALMKPSHVIVETMM

SEQ ID NO:67 Human (R)-3-hydroxybutyrate dehydrogenase nucleotide sequence

HUM222493 accession:NM_004051 CDS:224..1255

GGCACGAGGGCGGAGGCCGCAGGCCGCAGGAGTGCTGGTGGAGGGGCTTCCAGAAAGACCCTGCGGCAGCGCCCCCCCTCGGC
TCTCCCCGCAGGAGAGCGGGCACCTGCGCGGCGCCGGGTGAAGGCGAGAGCCTCGGCGAGCCCTCTGCAGCGGAGCCCCCTGC
CCATTTGGTTTTGGAACCACCGGGAGGAACTGGGCCATTCTAACACCCGTTGCTACCATGCTGGCCACCCGCCTCTCCAGACC
CCTGTCACGGCTCCCAGGAAAAACCCTAAGTGCCTGTGATAGAGAAAATGGAGCAAGACGCCCACTATTGCTTGGTTCTACTT
CCTTTATCCCGATTGGCCGTCGGACTTATGCCAGTGCGGCGGAGCCGGTTGGCAGCAAAGCTGTCCTGGTCACAGGCTGTGAC
TCTGGATTTGGGTTCTCATTGGCCAAGCATCTGCATTCAAAAGGCTTCCTTGTGTTTGCTGGCTGCTTGATGAAGGACAAAGG
CCATGATGGGGTCAAGGAGCTGGACAGCCTAAACAGTGACCGATTGAGAACCGTCCAGCTCAATGTCTGCAGCAGCGAAGAGG
TGGAGAAAGTGGTGGAGATTGTCCGCTCGAGCCTGAAGGACCCTGAGAAAGGCATGTGGGGCCTCGTTAACAATGCCGGCATC
TCAACGTTCGGGGAGGTGGAGTTCACCAGCCTGGAGACCTACAAGCAGGTGGCAGAAGTGAACCTTTGGGGCACAGTGCGGAT
GACGAAATCCTTTCTCCCCCTCATCCGAAGGGCCAAAGGCCGCGTCGTCAATATCAGCAGCATGCTGGGCCGCATGGCCAACC
CGGCCCGCTCCCCGTACTGCATCACCAAGTTCGGGGTAGAGGCTTTCTCGGACTGCCTGCGCTATGAGATGTACCCCCTGGGC
GTGAAGGTCAGCGTGGTGGAGCCCGGCAACTTCATCGCTGCCACCAGCCTTTACAGCCCTGAGAGCATTCAGGCCATCGCCAA
GAAGATGTGGGAGGAGCTGCCTGAGGTCGTGCGCAAGGACTACGGCAAGAAGTACTTTGATGAAAAGATCGCCAAGATGGAGA
CCTACTGCAGCAGTGGCTCCACAGACACGTCCCCTGTCATCGATGCTGTCACACACGCCCTGACCGCCACCACCCCCTACACC
CGCTACCACCCCATGGACTACTACTGGTGGCTGCGAATGCAGATCATGACCCACTTGCCTGGAGCCATCTCCGACATGATCTA
CATCCGCTGAAGAGTCTCGCTGTGGCCTCTGTCAGGGATCCCTGGTGGAAGGGGAGGGGAGGGAGGAACCCATATAGTCAACT
CTTGATTATCCACGTGTGGATTATCCACCATGCCAGGAAGACCCATAACTGGTTTTAACACTAACTAGAGGGAATGACTTCTT

TGCATAGTGAGTGACTTGGGCCTTCACAAACAGGGTGTGGAGTGGCAGGCAGAGGCCTCTAAATCTCAGGGCAAACATGGTGA
ATCTATCTCTCCGGAGATAATTTCATACAGAGATTTTAAGAAAACATCTTTATATTAAAAACAGATCTCATTTGATCCTTAAA
AAAAAAAAAAAAAAAA

SEQ ID NO:68 Human (R)-3-hydroxybutyrate dehydrogenase polypeptide sequence

protein_id:gi17738292

MLATRLSRPLSRLPGKTLSACDRENGARRPLLLGSTSFIPIGRRTYASAAEPVGSKAVLVTGCDSGFGFSLAKHL
HSKGFLVFAGCLMKDKGHDGVKELDSLNSDRLRTVQLNVCSSEEVEKVVEIVRSSLKDPEKGMWGLVNNAGISTF
GEVEFTSLETYKQVAEVNLWGTVRMTKSFLPLIRRAKGRVVNISSMLGRMANPARSPYCITKFGVEAFSDCLRYE
MYPLGVKVSVVEPGNFIAATSLYSPESIQAIAKKMWEELPEVVRKDYGKKYFDEKIAKMETYCSSGSTDTSPVID
AVTHALTATTPYTRYHPMDYYWWLRMQIMTHLPGAISDMIYIR

SEQ ID NO:69 Mouse(R)-3-hydroxybutyrate dehydrogenase nucleotide sequence

accession:BC027063

GGACAAAGGTGATGCTGGGGTCAAGGAACTGGACAGCTTGAAGAGTGACCGACTGAGAACCATCCAGCTCAATGT
CTGCAACAGTGAAGAGGTGGAGAAGGCGGTGGAGACGATCCGCTCCGGCCTGAAAGATCCTGAGAAGGGAATGTG
GGGCCTGGTTAACAACGCAGGCATCTCAACGTTTGGGGAGGTGGAGTTCACCAGCATGGAGACATATAAGGAGGT
GGCTGAAGTGAACCTCTGGGGAACCGTGCGCACCACAAAATCCTTCCTTCCCCTTCTCCGAAGAGCCAAAGGTCG
CGTCGTTAACATCAGCAGCATGCTGGGCCGCATGGCCAACCCCGCCCGCTCGCCATACTGCATCACCAAGTTTGG
GGTCGAGGCTTTCTCGGACTGCCTGCGCTATGAGATGCACCCTCTGGGTGTCAAGGTCAGTGTGGTGGAACCTGG
CAACTTCATAGCGGCCACCAGTCTCTACAGCCCCGAGCGCATCCAGGCCATCGCCAAGAAGATGTGGGATGACCT
GCCTGAGGTCGTCCGCAAGGACTATGGCAGGAAGTACTTCGATGAAAAGATTGCCAAGATGGAAACCTACTGCAA
CAGCGGTTCCACAGATACTTCCTCTGTCATCAACGCTGTCACACACGCCTTGACCGCCGCCACCCCGTATACCCG
CTACCATCCCATGGACTACTACTGGTGGCTTCGGATGCAGATCATGACCCATTTTCCTGGAGCCATCTCTGACAA
GATCTACATACACTGAAGAGCTGAAGAGGTCCCTTCGGTCTCCGCCAGGGAACCTGGTGGGAGGGAGAAAGATGA
GGGGAGGGAGTTTACCTTTTGATTAGCTATTGAGGATTACCCACTGTCTTAGGAAGACCTATTTTAACCTTACGT
GTTCAATGTGGTGAATGGTTTGGGCCTTCACAAATTAGGGGGGGGGGGCGGAGGGCGCAGGTGGGTGGCCCTAAA
CCTCAGGGCCAATATGGTGCTTCTATCTATCTCGAGTTGATTTTATATAAAGATTTGTGGGGAAATATCTTTATA
TTAAAAGCAGGTTATTAGAATAGAATCCAAAATCATTTTCCAGCCAAAACATCCATTCGAAATCTGTATCCCATT
TGATCCTTATGTAAGTCTCATGAGTAAACAGAACAGAATTTTTTTTTTCTTGTGTGCATGAAAGAATTTGCAGAT
CGCAGAGGACATACGAGACACCTCTTTCATTGTGTCCACGGAGTCCCGCCAGTGTTACGGCAAAGGCAAATCACA
TTTGTGTCCCACAGACACTTGAACCCATCAGTCCAGTAACCCTGTGACCAACTCTGTACCTTCTCCTGAGCCAGT
CACACCAAAGGTCACTGTGTGCTATGTCTCTGTGCGTCCGTAGCTCTGTGTGACTGGTGGCCAGCAGTCAGTGAC
TCTCTGCTGGCTCCAGGTGGGGGAATCCAGAGACTTTTCAGCTGAGATCTTGGCATTCTCATTAAAGATTCGAGT
TAGGTCTGGGTGAAGATGCTGTCCGGCTAAGAGCGCAGCTTGGTTTTGCCTAGGACAGGATTGGTGCTATGCTTG
GTGCTGCAAACAGACCAGTGGTGCCAAGGCTGGGCACTGAGACACTTGCCCAGCAATGGGTCTAGATGCCTGTTG
TCTTGTGTGCTCATGTGGTGCTCCCACATGTGGGTGCGTGTGTGCATGCACTCACACACACACACACACACACAT

CACACACACACACACACATCACACACACACACACACCTGCTCCATAGACTTCAGGGTGGTCACCTCTTCTT
TGTATTGGGAACTTCTTTTTAATTAAACTGAGACACAGTTAGAGAGCCTGTGTTCTCAATCAAGGGACTTTTGCA
TTTGAAGGCTGCTTGTCCCTGAAGTTTCCTAGGGTCTCAGTATTTGGATCCAAACCAAATCCCACCACGTTCCAG
GTGGCAGCAAGTCTTGGGCCGGGTATTTAAGTGCCAGCTTTACACACATCTCAGCTTTACACTTTTGTGCATCTT
GTTGCAAAGTCTAGGACTGCCACTAGAGGGCGCGCTGCCCCCTCAACTGGAGCCTGCTCAGGCCCGGGCGTTTTC
GTTCACACAAACTTGGGGTCTTTTCAAGAGTGTTTGACCACCTACTTGGACACTGCCAGGGAACAAAGAGAAGAG
CAAAGACCCCCTTGGAAACCGATCCTACACTCCTGGCAGTGTCTAGCCTGAAACTGAAGCCCAGCGCCAGGAGAA
AGCAAAGGAACCTGGACAGCCACAGGCGGGTGCAGGCAGTGCTGAGACAAAGAGGGTCCCACAGAGAGCGAATTC
AGCCTGCCGGTTTGGGCTTTTAACCCCTCTGGATACAAACAGAGGTGCACTGTTCTAGCTCCTGTCTTCAAAGCA
AAGTAGATAGGGCCTGAGAGGGAAGGTGAGAGGGAGCCAGGGCCCCAGGGTCCACGAATTTACCTGACAGCGGGA
TGCATTTGTACTGCAGAGCCTGCCTCCTGCTGGCGTCTTTCAGTGGCATTTTACACCTTGGGAGAATTTGTATCC
GTGTTTAATAAAGAGATTGGTCATAACAAAAAAAAAAAAAA

SEQ ID NO:70 Mouse (R)-3-hydroxybutyrate dehydrogenase polypeptide sequence

accession:gi20071589

DKGDAGVKELDSLKSDRLRTIQLNVCNSEEVEKAVETIRSGLKDPEKGMWGLVNNAGISTFGEVEFTSMETYKEV
AEVNLWGTVRTTKSFLPLLRRAKGRVVNISSMLGRMANPARSPYCITKFGVEAFSDCLRYEMHPLGVKVSVVEPG
NFIAATSLYSPERIQAIAKKMWDDLPEVVRKDYGRKYFDEKIAKMETYCNSGSTDTSSVINAVTHALTAATPYTR
YHPMDYYWWLRMQIMTHFPGAISDKIYIH

SEQ ID NO:71 Rat (R)-3-hydroxybutyrate dehydrogenase nucleotide sequence

accession:NM_053995

CCCTCAATAGCCACACTATTTATTTTATTTCAATTAAAAATTTCTTCCCAAACCTTTCCTGCACCTCCCTCACCC
AAAACTATAAACTCGGTGCCATGATGCTGGCCGCCCGTCTTTCCAGACCCCTGTCACAGCTCCCAGGAAAAGCTC
TAAGTGTCTGTGATAGAGAAAATGGGACAAGACACACACTGTTGTTTTACCCAGCTTCTTTCAGCCCTGACACCC
GTCGGACCTACACCAGCCAGGCAGATGCGGCTAGTGGCAAAGCTGTCCTGGTTACAGGCTGTGACTCTGGATTTG
GGTTCTCTTTGGCCAAGCATCTACACTCAAAAGGTTTCCTTGTATTTGCCGGATGTTTGTTGAAGGAACAAGGCG
ATGCTGGGGTCAGGGAGCTGGACAGCCTGAAGAGTGACCGGCTGAGAACCATCCAGCTCAATGTCTGCAACAGTG
AGGAGGTGGAGAAAGCGGTGGAGACCGTCCGCTCCGGCCTGAAGGATCCTGAGAAGGGAATGTGGGGCCTGGTTA
ACAACGCAGGCATCTCAACGTTTGGGGAGGTGGAGTTCACTAGCATGGAGACGTATAAGGAGGTGGCCGAAGTGA
ACCTCTGGGGAACTGTGCGCACAACAAAATCCTTCCTTCCCCTTCTCCGAAGAGCCAAAGGCCGTGTTGTTAACA
TCAGCAGCATGCTGGGTCGCATGGCCAACCCAGCCCGCTCACCATACTGCATCACCAAGTTTGGGGTAGAGGCTT
TCTCGGACTGCCTACGCTATGAGATGCACCCTCTGGGTGTGAAGGTCAGTGTGGTGGAGCCTGGCAACTTCATAG
CTGCCACCAGCCTCTATAGCCCTGAGCGTATCCAGGCCATTGCCAAGAAGATGTGGGATGAGCTGCCAGAGGTCG
TCCGCAAAGACTATGGCAAGAAGTACTTCGATGAAAAGATTGCCAAGATGGAGACCTACTGCAACAGCGGTTCCA
CCGATACGTCCTCCGTCATCAACGCTGTCACCCATGCCCTGACTGCTGCCACCCCTTATACCCGCTACCATCCCA
TGGACTACTACTGGTGGCTGCGGATGCAGGTCATGACCCATTTTCCTGGAGCCATCTCTGACAAGATCTACATAC

ACTGAAGAGCTGAAGAGGTCCCTGCAGCCTCTGCCAGGGAGCCTGATGGGAGGGAGTTCATACAGTTATCTTTTG
ATTAACCATTGTGGGTTGTCCACTGTCTTAGGAAGACCTATTTTAACCTTACGTGTTCAATGTGGTGAATGGTTT
GGGCCTTCACAAATACAGGGCACTGGTGGGTGGCCCTAACCCTCAAGGCCAATATGGTGCTTCTATCTGTCTATC
TAGAGTTGATTTTATATAAAGATTTGTGGGAAATACCTTTATATTAAAGACGTTATTAGAATAGAAAAAA

SEQ ID NO:72 Rat (R)-3-hydroxybutyrate dehydrogenase polypeptide sequence

accession:gi16758902

MMLAARLSRPLSQLPGKALSVCDRENGTRHTLLFYPASFSPDTRRTYTSQADAASGKAVLVTGCDSGFGFSLAKH
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SEQ ID NO:73 Human aldehyde reductase nucleotide sequence

HUM223359 accession: J04794 + CDS:61..1038

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SEQ ID NO:74 Human aldehyde reductase polypeptide sequence

protein_id:gi178481

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SEQ ID NO:103 Human TRP-MET nucleic acid sequence

gi|187558|gb|J02958.1| CDS:195..4421

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SEQ ID NO:104 Human TRP-MET polypeptide sequence

gi|307196|gb|AAA59591.1|

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SEQ ID NO:105 Mouse TRP-MET nucleic acid sequence

gi|6678867|ref|NM_008591.1| CDS:1..4140

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SEQ ID NO:106 Mouse TRP-MET polypeptide sequence

gi|6678868|ref|NP_032617.1|

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SEQ ID NO:107 Rat TRP-MET nucleic acid sequence

gi|13928699|ref|NM_031517.1|

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SEQ ID NO:108 Rat TRP-MET polypeptide sequence

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